Schistosomus Reflexus Syndrome: A Heritable Defect in Ruminants

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With 7 figures and 3 tables

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Summary

Schistosomus reflexus (SR) is a rare and fatal congenital disorder. Primarily observed in ruminants, its defining features include spinal inversion, exposure of the abdominal viscera because of a fissure of the ventral abdominal wall, limb ankylosis, positioning of the limbs adjacent to the skull and, lung and diaphragm hypoplasia. Variable components of SR include scoliosis, cleft sternum, exposure of thoracic viscera, and abnormalities of the digestive and urogenital systems. This report presents the findings from an anatomical analysis of a female Holstein SR calf with thoracochisis, scoliosis and anomalies of the appendicular skeleton, cardiovascular, respiratory, digestive and urogenital systems. Many of these malformations have not been previously reported. The reproductive tract of this case is particularly unique, displaying Muellerian duct abnormalities. These abnormalities suggest SR occurs as early as the post-gastrulation embryo and involves the intermediate mesoderm. Preliminary analysis of associated cases suggests that SR has a genetic aetiology.

Introduction

Schistosomus reflexus (SR) is a rare type of fetal monstrosity seen primarily in cattle (Knight, 1996). This fatal congenital syndrome is characterized by the presence of exposed abdominal and sometimes thoracic viscera (schistosomus), and marked spinal inversion producing a distinctive ventral convex curvature (reflexus; Roberts, 1986). The condition belongs to the family of defects involving incomplete closure of the ventral body wall. The ‘schistosomus’ aspect of the syndrome, i.e. the presence of a congenital chistostocia, is manifested in many species (Bishnoi et al., 1987; Pivnick et al., 1998). Conversely, the ‘reflexus’ component of the disorder is limited to only a few species. In fact, it has been suggested by Bezek and Frazer (1994) that this anomaly is restricted to ruminants. Manifestation of SR appears to thus far preclude humans; however, the human thoracochrominal syndrome (TAS) displays striking similarities (Pivnick et al., 1998).

The highest prevalence of SR is believed to occur in cattle (Knight, 1996), ranging from a low of 0.01% (Sloss and Johnston, 1967) to a high of 1.3% (Knight, 1996) of bovine dystocias. Such occurrences are costly to the cattle industry because of the reduction in the number of viable offspring, loss of milk production in dairy cases and cost of fetal extraction (Morrow, 1986).

The literature contains several reports of SR in occurrences of twin fetuses (Table 1). The discovery of four sets of twins included a SR calf in the retrospective study of 6901 cases of bovine dystocia suggests a positive association between twin embryos and SR (Knight, 1996). A set of twin calves has been described of which one was freemartin, and one SR (Cavalieri and Farin, 1999).

Relatively few SR case reports have been presented. The few published reports typically lack detailed anatomical analyses. Moreover, conflicting understandings of the criteria for a case of SR are evident. In the present report, only cases displaying both exposed viscera and spinal inversion are considered to be true SR. However, even these defining features of the syndrome are found to be highly variable in the extent of visceral exposure and degree of spinal inversion (Table 2). Previously, several cases had been categorized as SR, but lacked the ‘reflexus’ component, i.e. the presence of spinal inversion (Iyer, 1983; Mukasa-Mugerwa and Bekele, 1989). The ‘reflexus’ component alone has been described using such varying terminology as dorsiflexion, dorsal flexion, retroflexion and inversion. The present report has selected ‘spinal inversion’ as the term most reasonable and least ambiguous in describing this spinal anomaly. Accordingly, there is a need for a consensus on the defining features of the SR syndrome.

The present report is a detailed anatomical account of a SR calf showing both similarities to the literature as well as associated anomalies not previously reported (Table 3). By summarizing the features of previous SR case reports and comparing these with the characteristics of the present case, this report attempts to remove the inconsistencies surrounding the definition of SR. This is achieved by the proposal of a set of integral features for the condition as well as a set of consistent terminology to describe these features.

Materials and Methods

A full-term female SR calf was delivered by caesarean section from a Holstein cow with dystocia. A functioning heart was felt prior to caesarean section; however, the calf did not survive the delivery. The calf was subsequently presented to the Ontario Veterinary College (OVC) for postmortem analysis. On arrival at OVC, radiographs and digital photographs were taken of the SR calf. The calf was then immersed in 10% formaldehyde, and stored until dissection commenced. Anatomical analysis of the specimen was carried out by means of gross dissection. Data were recorded using digital photography and radiography.

Observations

This case of SR had multiple congenital anomalies. In fact, all organs and systems displayed an irregular orientation, with the exception of the head and neck (Fig. 1). Spinal inversion was
Current case

Rib fusion, dorsally inverted forelimb, hypoplastic scapula, abnormally oriented heart, large patent ductus arteriosus, caudal vena cava embedded in left lobe of liver, abnormally oriented and lobed liver, abnormal positioning of lesser omentum, abnormally oriented stomach, twist in oesophagus and vagus nerve, blind-ended duodenal sac, distended descending colon, thin-walled and distended rectum, grossly distended left uterine horn, right uterine horn agenesis, thin-walled and distended uterine body separated by spiral-like septum, urorethral communication, cervical and vaginal agenesis, enlarged neck of bladder, distended urethra with abnormal longitudinal folds and erectile tissue.

Variable presence

Imperforate anus (Dennis and Meyer, 1965), non-union of pubic symphyses (Smith, 1969), cleft sternum (Bedford, 1967), hydronephrosis, cryptorchidism, arthrogryposis (Dennis, 1972), limbs and head encapsulated by skin (Rai et al., 1975), scoliosis, reduced number of thoracic vertebrae and ribs (Fatimah et al., 1981), hydrocephalus, deformed pelvis, umbilical hernia, enlarged liver, absence of dorsal prominence of tongue, depression at frontonasal union, caudal frontal part of frontal torus raised, tufts of hair on vulva, enlarged liver (Cavalieri and Farin, 1999), cystic liver (Roberts, 1986)

Status of characteristic

Always present (defining)

Spinal inversion, exposure of abdominal viscera, limb ankylosis, positioning of the legs adjacent to the skull, lung and diaphragm hypoplasia

Variable presence

Imperforate anus (Dennis and Meyer, 1965), non-union of pubic symphyses (Smith, 1969), cleft sternum (Bedford, 1967), hydronephrosis, cryptorchidism, arthrogryposis (Dennis, 1972), limbs and head encapsulated by skin (Rai et al., 1975), scoliosis, reduced number of thoracic vertebrae and ribs (Fatimah et al., 1981), hydrocephalus, deformed pelvis, umbilical hernia, enlarged liver, absence of dorsal prominence of tongue, depression at frontonasal union, caudal frontal part of frontal torus raised, tufts of hair on vulva, enlarged liver (Cavalieri and Farin, 1999), cystic liver (Roberts, 1986)

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Table 1. Recorded cases of schistosomus reflexus (SR) in births of twin offspring

<table>
<thead>
<tr>
<th>Author</th>
<th>Species</th>
<th>Status of non-SR twin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Williams (1952)</td>
<td>Bovine</td>
<td>Normal</td>
</tr>
<tr>
<td>Morton (1968)</td>
<td>Bovine</td>
<td>Normal</td>
</tr>
<tr>
<td>Knight (1996)</td>
<td>Bovine</td>
<td>Stillborn</td>
</tr>
<tr>
<td>Knight (1996)</td>
<td>Bovine</td>
<td>Normal</td>
</tr>
<tr>
<td>Knight (1996)</td>
<td>Bovine</td>
<td>Normal</td>
</tr>
<tr>
<td>Cavalieri and Farin (1999)</td>
<td>Bovine</td>
<td>Freemartin</td>
</tr>
<tr>
<td>Bedford (1967)</td>
<td>Caprine</td>
<td>Normal</td>
</tr>
<tr>
<td>Smith (1969)</td>
<td>Ovine</td>
<td>Normal</td>
</tr>
<tr>
<td>Dennis (1972)</td>
<td>Ovine</td>
<td>Conjoined</td>
</tr>
</tbody>
</table>

Table 2. Reported variability of two defining characteristics of schistosomus reflexus (SR); i.e. extent of visceral exposure and degree of spinal inversion

<table>
<thead>
<tr>
<th>Author</th>
<th>Extent of visceral exposure</th>
<th>Degree of spinal inversion and associated vertebral column defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dennis and Meyer (1965)</td>
<td>Abdominal</td>
<td>Ankylosis</td>
</tr>
<tr>
<td>Smith (1969)</td>
<td>Thoracoabdominal</td>
<td>Lateral reflection and ankylosis in lumbar and thoracic regions</td>
</tr>
<tr>
<td>Bedford (1967)</td>
<td>Thoracoabdominal</td>
<td>Acute angulation and ankylosis of lumbar vertebrae</td>
</tr>
<tr>
<td>Dennis (1972)</td>
<td>Abdominal</td>
<td>Kyphoscoliosis of thoracic vertebrae</td>
</tr>
<tr>
<td>Rai et al. (1975)</td>
<td>Abdominal</td>
<td>Acute angulation</td>
</tr>
<tr>
<td>Fatimah et al. (1981)</td>
<td>Abdominal</td>
<td>Left deviation at thoracolumbar junction</td>
</tr>
<tr>
<td>Bugalia et al. (1982)</td>
<td>Abdominal</td>
<td>Deviation of head to right</td>
</tr>
<tr>
<td>Bezek and Frazer (1994)</td>
<td>Thoracoabdominal</td>
<td>None reported</td>
</tr>
<tr>
<td>Cavalieri and Farin (1999)</td>
<td>Thoracoabdominal</td>
<td>Lordosis</td>
</tr>
</tbody>
</table>

Table 3. Summary of schistosomus reflexus (SR) syndrome: defining characteristics, variable features previously reported and characteristics of the present case

<table>
<thead>
<tr>
<th>Status of characteristic</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Always present (defining)</td>
<td>Spinal inversion, exposure of abdominal viscera, limb ankylosis, positioning of the legs adjacent to the skull, lung and diaphragm hypoplasia</td>
</tr>
<tr>
<td>Variable presence</td>
<td>Imperforate anus (Dennis and Meyer, 1965), non-union of pubic symphyses (Smith, 1969), cleft sternum (Bedford, 1967), hydronephrosis, cryptorchidism, arthrogryposis (Dennis, 1972), limbs and head encapsulated by skin (Rai et al., 1975), scoliosis, reduced number of thoracic vertebrae and ribs (Fatimah et al., 1981), hydrocephalus, deformed pelvis, umbilical hernia, enlarged liver, absence of dorsal prominence of tongue, depression at frontonasal union, caudal frontal part of frontal torus raised, tufts of hair on vulva, enlarged liver (Bugalia et al., 1982), bifurcation of scrotum, atresia ani, prognathia, right deviated wry nose (Cavalieri and Farin, 1999), cystic liver (Roberts, 1986)</td>
</tr>
<tr>
<td>Current case</td>
<td>Rib fusion, dorsally inverted forelimb, hypoplastic scapula, abnormally oriented heart, large patent ductus arteriosus, caudal vena cava embedded in left lobe of liver, abnormally oriented and lobed liver, abnormal positioning of lesser omentum, abnormally oriented stomach, twist in oesophagus and vagus nerve, blind-ended duodenal sac, distended descending colon, thin-walled and distended rectum, grossly distended left uterine horn, right uterine horn agenesis, thin-walled and distended uterine body separated by spiral-like septum, urorethral communication, cervical and vaginal agenesis, enlarged neck of bladder, distended urethra with abnormal longitudinal folds and erectile tissue</td>
</tr>
</tbody>
</table>
left ventricle, paraconal inter-ventricular groove, right ventricle and pulmonary trunk were clearly visible. In addition, the heart was rotated cranially in its sagittal plane by approximately 45°, bringing the apex of the heart in close approximation to the neck. All major vessels followed the abnormal curvature of the spine, and despite the abnormal heart orientation, arrived at their appropriate destinations. The atria, auricles, atrioventricular valves, ventricles and semilunar valves of the aorta and pulmonary artery were normal. There was, however, a large, patent ductus arteriosus.

The lungs had normal lobation, but were extremely hypoplastic (Fig. 4). The left lung was smaller than the right. The combined dorsal surface of both lungs measured 11.5 cm from right to left margin. From cranial margin to caudal extent, the dorsal surfaces of both left and right lungs measured 13.8 cm. Dorsal surface impressions were absent in both lungs, and the cardiac notch of the left lung was abnormally small. The diaphragm was absent except for a remnant adjacent to the caudal vena cava (Fig. 4).

An enlarged, abnormally oriented, cystic liver covered both the lungs and the right ventricle of the heart (Fig. 5). The diaphragmatic (cranial) surface measured 28.2 cm from left to right lateral lobes, and the widest cranial to caudal margin measured 16.8 cm. The liver was rotated approximately 45° in its sagittal plane so that the left lobe was positioned ventrocranially. In addition, the cranial surface of the liver presented
Two fluid-filled cysts, measuring 10.7 and 2.5 cm in diameter, were observed on the cranial surface. They were positioned near the dorsal margin at the junction of the right and left lobes, the larger cyst being in a more dorsal position than the smaller cyst. Just medial to the larger cyst was the umbilical vein. In addition, the liver was abnormally shaped and lobed. A constriction at the junction of the right and left lobes gave the liver an appearance resembling a pair of wings. Abnormal folds of tissue were observed on the diaphragmatic surface to the right of the liver’s midline. On the visceral surface, an abnormally shaped quadrate lobe was located just to the left of the hepatic portal vein. No caudate lobe or renal impression was distinguishable. The caudal vena cava was completely embedded within the substance of the left lobe. A rudimentary lesser omentum was identified; however, it was abnormally positioned and did not connect to the abomasum, omasum, or duodenum.

The stomach of the calf was rotated approximately 180° in its coronal plane, such that the abomasum and omasum were abnormally located on the left side, the rumen caudally and the greater omentum dorsally. The stomach was distended, but grossly normal. A normal spleen was identified adjacent to the dorsal sac of the rumen; however, it was located on the right side of the calf, just distal to the liver. A twist in the oesophagus just cranial to its entrance into the stomach was observed. The accompanying vagus nerve displayed a similar twisting.

The small and large intestine appeared grossly normal, with the exception of a blind-ended duodenal sac at the approximate location of the cranial duodenal flexure and sigmoid flexure (Fig. 6). The sac was 6.1 cm deep, and 4.4 cm wide. A portion of descending colon just prior to the termination point of the ventral body wall fissure was distended with meconium. Distal to this was a segment of normal colon, and then a thin-walled rectum also distended with meconium (Fig. 7). The anus was present and patent.

The kidneys, ureters and adrenal glands were all exposed and positioned on the right side of the calf. They were located caudal to the spiral loop of the ascending colon, and adjacent to the spinal column. They appeared to have normal morphology. Ventral to the distended portion of colon, a large, blind-ended sac was identified as the left uterine horn (Fig. 7a,b). A rudimentary left ovary was located in the fascia attached to the distal end of the left horn. Despite a careful investigation, no evidence of a right uterine horn or ovary could be identified. The apparent body of the uterus was grossly distended and thin walled. Internally, it was partially divided by an unusual spiral-like septum; thus it was a form of ‘septate uterus’. The body of the uterus communicated with the urethra via a ‘pinhole’-sized fistula located 15.5 cm from the vulva (Fig. 7b). No cervix or vagina was found associated with or distal to this communication. However, normal female
of the abdominal viscera, spinal inversion and the positioning of the limbs adjacent to the head and their subsequent ankylosis. As shown by this and other cases, the severe spinal inversion often results in the occiput of the head lying in close approximation to the sacrum (Dennis and Meyer, 1965; Fatimah et al., 1981; Roberts, 1986) and causes the orientation irregularities seen among the organs and organ systems (Rai et al., 1975; Cavalieri and Farin, 1999).

The hypoplastic lungs, and pulmonary lobe abnormalities seen in this specimen have also been reported in other cases (Dennis and Meyer, 1965; Fatimah et al., 1981). Dennis and Meyer (1965) specifically reported that the lungs in their case were approximately half of the normal size. Thus, the regular occurrence of pulmonary hypoplasia in SR cases suggests that it too may be a distinguishing feature of the condition.

The presence of an incomplete diaphragm has been consistently reported in cases of SR (Bedford, 1967; Cavalieri and Farin, 1999). It is observed in SR cases with only abdominal fissures (Bugalia et al., 1982) as well as in those, such as the present that display thoracoabdominal fissures. Hence, diaphragmatic hypoplasia appears to be another consistent feature of SR.

From the variability in both the extent of visceral exposure and degree of spinal inversion it is apparent that even the defining features of SR manifest differently among cases. In the present case, the failure of the ventral thorax to close resulted in a complete sternal cleft, reflected rib cage and exposure of thoracic viscera. These observations are consistent with other studies that report both schistothorax and schisto-coelia (Knight, 1996; Cavalieri and Farin, 1999). However, cases have been presented that have only an abdominal fissure (Table 2). The presence of an exposed heart in this case correlates with other SR cases that had clefts of the sternum (Bedford, 1967; Smith, 1969; Bezek and Frazer, 1994; Cavalieri and Farin, 1999).

The present case displays spinal inversion affecting both the thoracic and lumbar vertebrae. However, past case reports have shown considerable variation in the degree and extent of spinal inversion (Table 2). Cases such as the present one, frequently present ankylosis of the spine, making spinal manipulation extremely difficult (Dennis and Meyer, 1965; Fatimah et al., 1981). The presence of scoliosis in this case and others appears to be a variable feature of SR. The thoracic portion of the spinal arch, in combination with the cleft sternum, is clearly responsible for the abnormal presentation of the ribs, abnormal passage of major vessels and the abnormal curvature observed in both the aorta and caudal vena cava.

A wide variety of other structural abnormalities are frequently observed in cases of SR. Many of these were also observed in the present case, but others were not (Table 3). Deformation of the pelvis is a variable skeletal anomaly that results from the spinal inversion and compression between the inverted spine and the caudal bones of the skull (Dennis and Meyer, 1965; Bugalia et al., 1982; Roberts, 1986). Jubb and Kennedy (1963) have also found the occasional failure of the pubic symphysis to unite. Fatimah et al. (1981) reported a decrease in the number of thoracic and lumbar vertebrae in a bovine case. Hydrocephalus has also been observed (Bugalia et al., 1982). Bifurcation of the scrotum and imperforate anus were described in two cases (Dennis and Meyer, 1965; Cavalieri and Farin, 1999) and atresia ani and a bifurcated scrotum simultaneously occurred again in a case of conjoined
twin lambs (Dennis, 1972). The similarity of these three cases seems to suggest a potential link between SR, scrotum bifurcation and atresia ani. Dennis and Meyer (1965) also described bilateral cryptorchidism in their case of SR, as did Dennis (1972) in his case of conjoined twin lambs. Occasional enclosure of the limbs and head in skin from the reflected body wall has also been reported (Bedford, 1967; Roberts, 1986).

The present case had several unique abnormalities. This is the first known SR case to present female urogenital anomalies. These included a distended left uterine horn and body, and apparent agenesis of the right uterine horn, vagina and cervix. There was a rudimentary left and an absent right ovary, a uterourethral communication, and a dilated urethra. A spiral-like septum inside the apparent uterine body is likely a remnant of the fusion of the original pair of Mullerian ducts. Thus, the distended ‘body’ may have incorporated the right horn so that it was not recognizable as a distinct entity.

Other unique abnormalities were present in this case. This is the first known report of a cardiac orientation anomaly in association with SR. The caudal vena cava passed through the left lobe of the liver. The case is the first known report of a distal rib fusion and a hypoplastic scapula. These occurrences may be attributable to a localized restriction of growth, resulting from tissue compression at the point of spinal inversion. Digestive tract defects were numerous and included an abnormally lobed and oriented liver, a twisted oesophagus, an unusually oriented stomach, irregular lesser omentum, a blind-ended duodenal sac, a distended descending colon and a thin-walled, distended rectum. The only digestive system anomaly presented in this case that had been previously linked to SR was the enlarged and cystic liver (Fatimah et al., 1981; Roberts, 1986).

The embryological mechanism by which a SR fetus develops is unknown. However, it is reasonable to consider that the origin of ventral wall closure defects such as SR occur as early as the post-gastrulation embryo. Thus, the paraxial and lateral mesoderm, from which the ventral body is derived, are of particular interest. Simultaneous observation of urogenital defects with SR in this case and in previous cases (Dennis and Meyer, 1965; Cavalieri and Farin, 1999) indicates that intermediate mesoderm, the precursor for the urogenital system, may also be affected by the mechanism (Carlson, 1999).

 Syndromes similar to SR exist in other species (Pivnick et al., 1998). However, because they display distinctly different spinal malformations, they are classified using alternate terminology. It is possible that these syndromes may be variations of SR resulting from the expression of a similar gene. Indeed, a genetic origin for SR is supported by ablation studies for the genes transforming growth factor (TGF)-b2, -b3 (Dünker and Krieglstein, 2002) and Pitx2 (Kitamura et al., 1999). The localization of a TAS gene to the X chromosome suggests that SR may be an X-linked disorder (Parvari et al., 1999). The hypothesis of a genetic aetiology is further supported by epidemiological evidence of case clusters. Although the majority of cases in the literature are reports of single SR occurrences, other multiple cases within short time periods have been observed in veterinary practices (Higham, 1987; Shilleto, 1987), and even in a slaughterhouse (Holt, 1987).

Jackson (1987) reports clusters of cases, in which the same bull had sired the affected calves. This observation appears to contradict an X-linked aetiological hypothesis (Parvari et al., 1994), because a bull carrying the mutant allele of a SR gene on its X chromosome would not survive postpartum. Lastly, a total of 12 SR Holstein calves have subsequently been identified beginning with the present index case. The same bull appears on both sides of all their pedigrees. This would suggest an autosomal recessive form of inheritance (H. McClinchev and P. K. Basur, 2004, personal communication).

In conclusion, SR is a rare and fatal congenital abnormality most prevalent in cattle. It is a syndrome of defects with consistent and variable components. The defining features include spinal inversion, exposure of the abdominal viscera due to a fissure of the ventral abdominal wall, limb ankylosis, positioning of the limbs adjacent to the skull, as well as lung and diaphragm hypoplasia. Variable components of SR include scoliosis, cleft sternum, exposure of thoracic viscera, and abnormalities of the digestive and urogenital systems.

References
